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Pharmacological targets in the renal peritubular microenvironment: Implications for therapy for sepsis-induced acute kidney injury

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ABSTRACT

One of the most frequent and serious complications to develop in septic patients is acute kidney injury (AKI), a disorder characterized by a rapid failure of the kidneys to adequately filter the blood, regulate ion and water balance, and generate urine. AKI greatly worsens the already poor prognosis of sepsis and increases cost of care. To date, therapies have been mostly supportive; consequently there has been little change in the mortality rates over the last decade. This is due, at least in part, to the delay in establishing clinical evidence of an infection and the associated presence of the systemic inflammatory response syndrome and thus, a delay in initiating therapy. A second reason is a lack of understanding regarding the mechanisms leading to renal injury, which has hindered the development of more targeted therapies. In this review, we summarize recent studies, which have examined the development of renal injury during sepsis and propose how changes in the peritubular capillary microenvironment lead to and then perpetuate microcirculatory failure and tubular epithelial cell injury. We also discuss a number of potential therapeutic targets in the renal peritubular microenvironment, which may prevent or lessen injury and/or promote recovery.

Contents

1. Introduction

1.1. Sepsis and acute kidney injury

Sepsis is a condition characterized by a disseminated inflammatory response triggered by a bacterial, viral or fungal infection. The most recent statistics list sepsis as the 7th leading cause of all deaths in children 1–4 years of age and the 8th in adults 65–75 years of age[1] but it is the major cause of death among critically ill patients. Each year approximately 750,000 patients in the United States (Hotchkiss & Karl, 2003) and 18 million people worldwide are affected (Marshall et al., 2005). Mortality rates for sepsis range from 25% to

Abbreviations: AKI, acute kidney injury; RBF, renal blood flow; MAP, mean arterial pressure; GFR, glomerular filtration rate; LPS, lipopolysaccharide; CLP, cecal ligation and puncture; MMP, matrix metalloproteinase; S1P, sphingosine-1-phosphate; S1PR, sphingosine-1-phosphate receptor; SphK, sphingosine kinase; SOD, superoxide dismutase; iNOS, inducible nitric oxide synthase; NO, nitric oxide; ROS, reactive oxygen species; RNS, reactive nitrogen species; IR, ischemia–reperfusion; SIRT1, sirtuin-1; MnTMPyP, Mn(III)tetrakis(1-methyl-4-pyridyl)porphyrin, tetratosylate, hydroxide (MnTMPyP); TNF- α, tumor necrosis factor alpha; α-MSH, alpha-melanocyte stimulating hormone.

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[1] U.S. Census Bureau, Statistical Abstract of the United States: 2011.

70% and are correlated with the presence of hypotension (shock) and the development of an associated single or multi-organ failure (Russell, 2006). To date, therapies have been mostly supportive; consequently there has been little change in the mortality rates over the last decade. This is due, at least in part, to the delay in establishing clinical evidence of an infection and the associated presence of the systemic inflammatory response syndrome (SIRS) and thus, a delay in initiating therapy (Remick, 2007; Stearns-Kurosawa et al., 2011). A second reason is a lack of understanding regarding the mechanisms leading to the development of organ injury.

One of the most frequent and serious complications to develop in septic patients is acute kidney injury (AKI), a disorder characterized by a rapid failure of the kidneys to adequately filter the blood, regulate ion and water balance, and generate urine (Zarjou & Agarwal, 2011). AKI greatly worsens prognosis and increases cost of care. The incidence of AKI increases with the severity of sepsis (Heemskerk et al., 2009) and estimates are that AKI develops within the first 24 h in 64% of patients with severe sepsis and hypotension (Bagshaw et al., 2009). Strikingly, the mortality rate for septic patients with AKI is approximately doubled compared with sepsis alone. Thus, protecting the kidney could significantly reduce morbidity and mortality in patients with severe sepsis. Unfortunately, treatment of sepsis-induced AKI has advanced little during the last several decades (Ricci et al., 2011). This review will focus on recent studies, which suggest the therapeutic potential for targeting the renal microcirculatory microenvironment in treating or even preventing sepsis-induced AKI.

As mentioned earlier, effective therapy in the septic patient is hampered because therapy is usually begun only after the onset of symptoms (Russell, 2006). In fact, Kumar and co-investigators reviewed the medical records of 2700 patients with septic shock between 1989 and 2004 and showed that only approximately 50% of the patients received adequate antibiotic treatment within the first 6 h of hypotension and alarmingly, each hour of delay in initiating therapy decreased survival by 7.6% (Kumar et al., 2006). Since the symptoms of SIRS are initiated by an infection but are driven by endogenous mediators such as cytokines (Lam & Ng, 2008; Mera et al., 2011), treatments targeting cytokines have the potential for being effective but have not been successful clinically due, once again, to the delay in initiating therapy (Remick, 2007). Clearly, the time at which therapy is initiated has a profound impact on outcome and this is especially true with regard to the development of AKI (Dudley, 2004). Early goal-directed therapy (EGDT) (Rivers et al., 2001), consisting of antibiotics, fluid resuscitation and hemodynamic support in an attempt to protect organ perfusion, is being evaluated as a systematic approach to supportive care and does improve survival compared to standard supportive therapy (Rivers et al., 2008); however, mortality rates are still high even among adequately resuscitated patients (Otero et al., 2006; Lundy & Trzeciak, 2009). Evidence-based guidelines for care developed through the Surviving Sepsis Campaign (Dellinger et al., 2004) recommend approaching therapy in two phases: antibiotics and resuscitation within the first 6 h and management within the first 24 h (Levy et al., 2010). Still, therapy is primarily supportive utilizing broad-spectrum antibiotics, fluid resuscitation, pressor agents, lung-protective ventilation, and if necessary, dialysis.

1.2. Renal microcirculatory failure

Animal and human studies along with clinical observations support the view that maintaining systemic pressure per se is not necessarily sufficient to maintain organ perfusion in the septic patient. Clinical findings indicate that the severity of microvascular dysfunction correlates with patient mortality (Sakr et al., 2004; Vincent & De Backer, 2005) supporting the concept that maintaining the microcirculation is key to preserving organ function. In animal models the link between microcirculatory failure and organ injury is reasonably well established, at least for the renal microcirculation (Wu & Mayeux, 2007; Holthoff et al., 2010; Wang et al., 2011). Nevertheless, because direct measurements of the microcirculation in humans is difficult and generally limited to the skin or sublingual microcirculation using sidestream dark-field imaging (Spanos et al., 2010), while suggested, the value of preserving the microcirculation has not yet been directly proven in humans (Boerma & Ince, 2010). Studies using Doppler ultrasonography to monitor flow through the renal intralobular arteries in humans with sepsis did show that raising mean arterial pressure with norepinephrine to 75 mm Hg (above the renal autoregulatory pressure) reduced the resistance index suggesting improved perfusion of the renal microcirculation. However, increasing pressure further to 85 mm Hg did not result in additional improvement (Deruddre et al., 2007). Hence, the goal of hemodynamic support need not be to completely restore mean arterial pressure but rather to elevate it enough to preserve the microcirculation (Boerma & Ince, 2010). One caveat with regard to the kidney is that autoregulatory systems controlling the microcirculation can limit overall perfusion even when systemic blood pressure is near normal, as described later. Suffice it to say, progress toward uncovering new specific therapeutic targets to treat or prevent sepsis-induced AKI requires a better understanding regarding the mechanistic relationships between the changes in the peritubular microcirculation and the development of renal tubular injury.

1.3. Animal models of sepsis

Significant advances have been made in understanding the development of renal injury during sepsis through the use of small and large animal models. Unfortunately, there are no current animal models, which fully replicate all of the complexities of human sepsis. One of the most frequently used models in rodents is the cecal ligation and puncture (CLP) model of polymicrobial peritonitis (Rittirsch et al., 2009). Other models of sepsis such as administration of lipopolysaccharide (LPS) from the Gram negative bacterial cell wall and administration of live or killed bacteria have been used as well; however, the inflammatory response in LPS models is quite different from that initiated by live bacteria models and CLP in both the kinetics and magnitude of cytokine release (Miyaji et al., 2003) as well as the role of the TLR4 receptor (Dear et al., 2006; Kalakeche et al., 2011). The severity of sepsis and, to some extent, the severity of AKI can be manipulated in each of these models by changing the dose of LPS or bacteria or by changing the size and/or number of cecal punctures. Sepsis models in larger animals such as sheep (Langenberg et al., 2006; Ramchandra et al., 2009) and pigs (Chvojka et al., 2008; Brandt et al., 2009) have been used and can exhibit hemodynamic changes that are more similar to human sepsis than most rodent models. Of course these models are largely impractical for mechanistic studies and are best used in pre-clinical evaluations of new therapies. The reader is directed to excellent reviews on animal models of sepsis, which discuss the advantages, disadvantages and limitations of each (Remick & Ward, 2005; Doi et al., 2009; Dyson & Singer, 2009).

Whether or not changes in renal blood flow (RBF) in septic patients contribute to renal injury is still unclear. The primary reason for this is the scarcity of actual measurements of RBF in septic patients. Not surprisingly, measuring RBF in severely ill patients is rarely done. In the few patients where RBF has been measured, high variability in these measurements among patients hinders reliable conclusions regarding the state of RBF during the course of sepsis-induced AKI (Bradley et al., 1976; Brenner et al., 1990; Langenberg et al., 2005). Consequently, the relationships between mean arterial pressure (MAP), RBF and the development of AKI in these critically ill patients are unknown. Unfortunately, animal studies have only added to the controversy regarding changes in RBF during sepsis. In hyperdynamic models of sepsis in larger animals where heart rate and cardiac output are increased, which more closely mimic what is observed in septic patients, RBF may increase, decrease or remain unchanged. For example, RBF increases over time in sheep following *E. coli* infusion (Langenberg et al., 2006; Ramchandra et al., 2009); however, in pigs subjected to autologous fecal peritonitis, a model more closely resembling polymicrobial